Further, Applicants noted a couple of typographical errors in their December 13, 2002 Amendment and, thus, have corrected these typographical errors herein. Further Applicants have deleted the term "lipid-like" from claim 58, which the Examiner objected to in the Advisory Action.

IN THE SPECIFICATION:

Page 1, lines 1-4:

Method for developing, testing and using associates of macromolecules and complex aggregates for improved payload and controllable de/association rates

01

The present application claims the benefit of International Application No. PCT/EP98/06750, filed on October 23, 1998.

Page 9, line 1, before "DEFINITIONS", please add the following:

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 illustrates insulin adsorption on different ultra-deformable vesicles. Transfersomes, as a function of protein/lipid concentration ratio in the bulk. In the lower panel, absolute bound protein amount is shown. In the upper panel, relative amount of vesicle associated insulin is given, no short-term time-effect being observed in either case. (Examples 1-27 A)

02

Fig. 2 presents the results of insulin binding experiments with ultra-deformable Transfersomes containing cholate as a function of total lipid concentration in the bulk. (Examples 1-27 B)

Fig. 3 gives data on insulin binding to Transfersomes, with cholate as a membrane softener, as a function of relative protein/lipid concentration in the bulk and of binding (incubation) time. (Examples 1-27 C)

Fig. 4 exemplifies insulin association with (binding to) surfactant (cholate or Tween 80) containing Transfersomes, as a function of protein/lipid concentration ratio in the bulk. Absolute and relative amounts of bound protein is shown in the lower and upper panel, respectively, highlighting the effect of changing vesicle composition in case of dilution with a buffer without added cholate. Such a dilution is not influential when Transfersomes contain the less soluble Tween 80. (Examples 46-59)

D2 cont.

Fig. 5 provides the data that supports the view that insulin from a solution or protein powder (lyophilisate) binds with comparable efficiency to different Transfersome quantities. (Examples 72-76)

Fig. 6 compares the relative efficiency of insulin binding to conventional liposomes (SPC), to charged liposomes (SPC/SPG) and to charged Transfersomes (SPC/SPG/Tween 80). (Examples 77-92)

Fig. 7 illustrates the effect of increasing surface charge density, created by incorporating increasing relative amounts of charged phospholipid SPG into originally uncharged SPC/Tween (SPC/Tw) Transfersomes, on insulin association with extended surfaces of resulting vesicles. (Examples 96-100)

Fig. 8 offers information on insensitivity of insulin binding to the method used to manufacture ultradeformable vesicles. Transfersomes, as evidenced by the relatively constant relative amount of surface (vesicle) associated protein. (Examples 101-104)

Fig. 9 explores the effect of ultra-deformable vesicle composition (SPC + cholate; SPC + Tween 80), of insulin kind/source (human recombinant insulin in Actrapid solution; lyophilized

human insulin; porcine insulin in solution) of association (incubation) time (2 hours to 5 weeks) using plain SPC liposomes as negative control.

Fig. 10 illustrates binding of a larger protein, interferon alpha, on non-ionic (SPC/Tw80) and anionic (SPC/NaChol) ultradeformable vesicles as a function of protein/lipid concentration ratio in the bulk. (Examples 111-134)

D2 cont'd

Fig. 11 provides evidence for biological activity of insulin delivered transdermally with the aid of charged, highly adjustable lipid vesicles comprising a mixture of a phospholipid (SPC) and of an anionic biosurfactant (cholate), such that ensures original insulin binding to the extended vesicle surface. Change in the blood glucose level after insulin application on the skin at relative time zero directly reflects the effect of insulin in vivo.

Fig. 12 points to the effect of batch-to-batch variability for insulin from the same manufacturer in case of transdermal delivery of the drug in Transfersomes (Transfersulin) in vivo. Open symbols give the result of negative control experiment. --

---

IN THE DRAWINGS:

Enclosed, please find Figs. 7 and 8, with corrections shown in red. In Fig. 7, a typographical error was made wherein reference was made to examples 96-98 rather than examples 96-100. In Fig. 8, a typographical error was made wherein reference was made to examples 99-100 rather than examples 101-104.

IN THE CLAIMS:

Please amend claims 58, 60-62, 67-75, 86, 93-97, 100, 101, 105 111, 114, 124, 126, 128, 131, 143, 144, 151, 157, 158, 161 162, 169 and 172 to read as follows:

---

58. A combination of substances in a liquid medium comprising:

at least one first amphiphatic substance selected from lipids;

D3